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The application of extracorporeal shock wave therapy on stem cells therapy to treat various diseases

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Abstract

In the last ten years, stem cell (SC) therapy has been extensively used to treat a range of conditions such as degenerative illnesses, ischemia-related organ dysfunction, diabetes, and neurological disorders. However, the clinical application of these therapies is limited due to the poor survival and differentiation potential of stem cells (SCs). Extracorporeal shock wave therapy (ESWT), as a non-invasive therapy, has shown great application potential in enhancing the proliferation, differentiation, migration, and recruitment of stem cells, offering new possibilities for utilizing ESWT in conjunction with stem cells for the treatment of different systemic conditions. The review *provides* a detailed overview of the advances in using ESWT with SCs to treat musculoskeletal, cardiovascular, genitourinary, and nervous system conditions, suggesting that ESWT is a promising strategy for enhancing the efficacy of SC therapy for various diseases.

Keywords Extracorporeal shock wave therapy, Stem cells, Musculoskeletal diseases, Cardiovascular diseases, Genitourinary diseases, Nervous system diseases

Introduction

Stem cells, also known as SCs, are undifferentiated cells found in embryos, fetuses, and adults, giving rise to specialized cells that make up tissues and organs, and possessing the ability to renew themselves and differentiate into various cell types [1]. Specifically, Mesenchymal Stem Cells (MSCs), which are a type of versatile stem cells, have the ability to transform into various types of cells [2], including nerve cells, bone cells, hepatic cells and vascular endothelial cells [3–6]. MSCs are multipotent cells found in various human tissues, known for their unique biological properties including low immunogenicity, potent immunomodulatory and immunosuppressive capabilities, particularly homing ability [7]. In the process of homing, MSCs migrate to the site of injury to exert therapeutic effects primarily through paracrine mechanisms [8], releasing a diverse array of functional

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molecules such as growth factors, inflammatory factors, chemokines, and extracellular matrix (ECM) components [9] to promote nerve repairment, bone healing, liver repairment and revascularization. The preconditioning strategy can improve the humming of homing of MSCs. For instance, ESWT has been shown to enhance the homing of MSCs in vivo [10].

Although stem cell-based therapies hold promise for treatment, there are various technical obstacles to overcome, such as the poor retention and survival of stem cells in the damaged area post-transplantation, and the restricted effectiveness of neural differentiation. These bottlenecks ultimately restrict the therapeutic effects of SC treatments [11]. Hence, a new and effective approach is necessary to enhance the therapeutic effects of stem cell, especially MSCs. (Fig. 1)

Several preconditioning strategies have been used to improve the therapeutic effect of SCs on various diseases, including hypoxia, gene modification, culture environment improvement, thermosensitive hydrogel, and so on [12]. However, the above mentioned strategies have their own limitations, for instance, low efficiency, complex operation process, etc. A promising preconditioning strategy, which can not only promote the survival, paracrine and migration ability of SCs but also do not exert harmful effects, can be deemed as the most appropriate preconditioning method to treat various diseases. For intance, Extracorporeal shock wave therapy (ESWT) is a non-invasive, high-efficient and easy to operate therapeutic method.

Shock waves (SWs), ranging in frequency from 16 Hz to 20 MHz, are characterized by a brief period of intense positive amplitude followed by a prolonged period of low negative amplitude. This unique waveform allows for the delivery of energy to distant targets while minimizing the impact on surrounding tissue. Moreover, SWs, divided into concentrated and divergent types, exhibit characteristics such as elevated peak pressure (exceeding 100 MPa), rapid pressure increase (less than 10 ns), and brief duration (less than 10μs) [13].

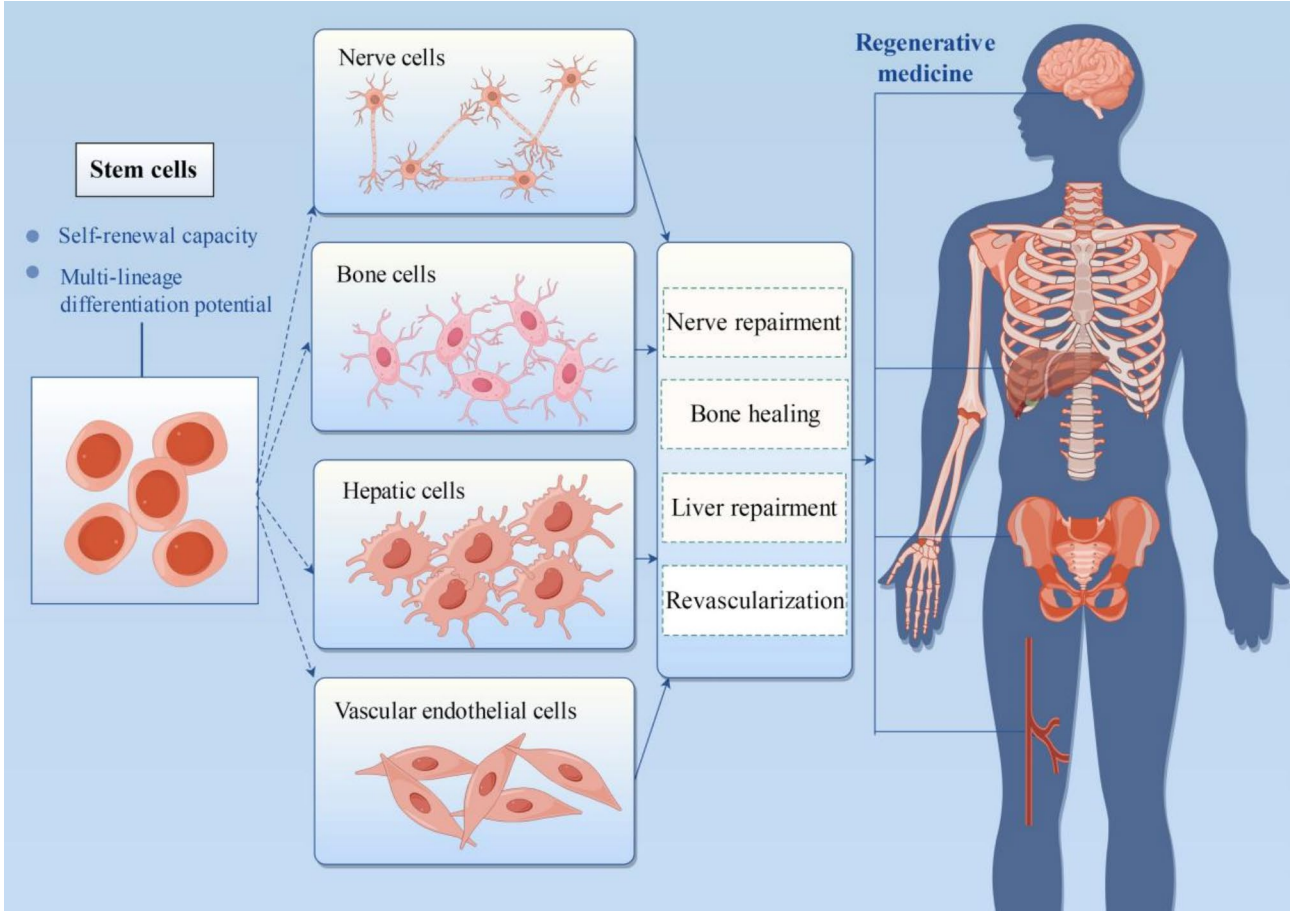

Fig. 1 SCs are featured by self-renewal capacity and multi-lineage differentiation potential. In particular, MSCs, as a type of multipotential stem cells, can differentiate into multipotential cells, including nerve cells, bone cells, hepatic cells and vascular endothelial cells. Stem cells are essential in regenerative medicine, serving as a source of cell regeneration and releasing paracrine factors to promote nerve repairment, bone healing, liver repairment and revascularization. (by figure draw)

ESWT is a non-invasive treatment form of physical therapy that applies tension and compression to tissue cells by passing through various mediums, which originates from extracorporeal shock wave lithotripsy (ESWL) [14]. ESWT systems can be categorized into three types based on their sound sources, including electro-hydraulic system, electromagnetic system, and piezoelectric system [15]. Various factors, such as air pressure, energy flux density (EFD) in mJ/mm^2, pulse count, and frequency in Hz, can impact the efficacy of ESWT. EFD is a measure of the energy intensity of shock waves in a specific location [16] and is used to classify ESWT into low, medium, and high energy levels depending on the EFD value. Additionally, the validity of ESWT is influenced by the depth of penetration [16]. Generally, focused ESWT (fESWT) can reach tissues up to a depth of 12 cm, while radial ESWT (rESWT) has a penetration depth of only 3–4 cm. The treatment site of ESWT can be determined through palpation, ultrasound, or x-rays [17]. Depending on the treatment area, patients may be positioned in prone, side lying, or sitting postures, and the intensity is adjusted according to the responses of patients [18].

When cells experience mechanical shock, they convert these mechanical signals into biogenic signals. This process triggers anti-inflammation, angiogenesis, immunomodulatory, cell proliferation and cartilage protection [19]. ESWT can trigger the extracellular matrix and cytoskeleton by stretching channels, serving as a mechanical force source [20]. The initiation of this process stimulates the proliferation, migration, and differentiation of stem cells, which are essential for the healing and regeneration of tissues [21]. ESWT has become increasingly popular as a treatment choice for a range of musculoskeletal conditions [22], including plantar fasciitis, tennis elbow [23], and nonunion [24], due to its positive impacts.

Following injury, mesenchymal stem cells demonstrate mobilization and subsequent homing to the site of injury [25]. These cells possess potent immunomodulatory and regenerative capabilities, positioning them as a promising therapeutic avenue for various clinical conditions [26]. ESWT has been demonstrated to enhance the migration and recruitment of a significant quantity of mesenchymal stem cells to the targeted regions [27]. Additionally, ESWT has been utilized in the treatment of wounds [28, 29] and urinary tract diseases [30, 31]. In summary, as is shown in Fig. 2, the applications of ESWT on SC therapy are mainly focusing on the musculoskeletal, cardiovascular, genitourinary, and nervous system conditions.

The mechanical stimulation of shock waves from ESWT can potentially influence the biological functions of stem cells, such as proliferation, migration, recruitment, and differentiation [32, 33].

First, the proliferation of cells is essential for the regeneration of tissues, and ESWT can enhance the proliferation of different kinds of stem cells, including bone marrow stem cells (BMSCs), adipose-derived stem cells (ADSCs), endothelial progenitor cells (EPCs), and neural stem cells (NSCs) [34, 35]. For example, ESWT enhances the proliferation of BMSCs and ADSCs in vitro, possibly involving the mitogen-activated protein kinase (MAPK) pathway, phosphatidylinositol-3 kinase/protein kinase B (PI3-K/Akt) pathway, and nuclear factor kappa B (NF-kB) signaling pathway [36, 37]. ESWT led to an elevation in the levels of vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8), subsequently promoting the proliferation of EPCs in individuals with coronary artery disease (CAD) [38]. In vitro studies have shown that ESWT can boost the proliferation of NSCs by activating the PI3K/Akt, Wnt/β-catenin, and Notch pathways [39]. Furthermore, the mechano-transduction signaling axis of mTOR- focal adhesion kinase (FAK) is activated by ESWT, leading to increased proliferation of MSCs in vitro [40].

Second, ESWT has also been shown to facilitate the migration and recruitment of numerous MSCs to affected area [27]. In vivo migration assays conducted by Xu et al. demonstrated that ESWT may promote the migration of ADSCs by upregulating the CXC chemokine ligand 5 /CXC chemokine receptor 2 (CXCL5/CXCR2) axis. Similarly, in a rat model of bladder dysfunction, ADSCs that underwent ESWT showed enhanced migration abilities to the damaged bladder in comparison to ADSCs that did not receive treatment [37]. Moreover, ESWT can directly or indirectly promote the production of transforming growth factor β1 (TGF-β1) and VEGF-A in wound tissue in a rat model with a segmental femoral defect, leading to the recruitment of MSCs [33].

Third, ESWT has been demonstrated to enhance the differentiation of different categories of stem cells, such as ADSCs, BMSCs, and NSCs. Schuh et al. demonstrated that ESWT increased the differentiation of human ADSCs into adipogenic, osteogenic, and Schwann-like cells at an energy level of 0.09 mJ/mm^2 in cell experiments [41]. ESWT can enhance the growth and differentiation of BMSCs into osteoprogenitor cells in a rat model by potentially increasing transforming growth factor beta-1 (TGF-β1) levels [34]. Moreover, ESWT promoted the differentiation of NSCs through the Wnt/β-catenin pathway, leading to the improvement of neurological function in rats after experiencing cerebral ischemia [42]. To sum up, ESWT can significantly promote the biological activities of stem cells, such as proliferation, differentiation, migration and recruitment. (Fig. 3).

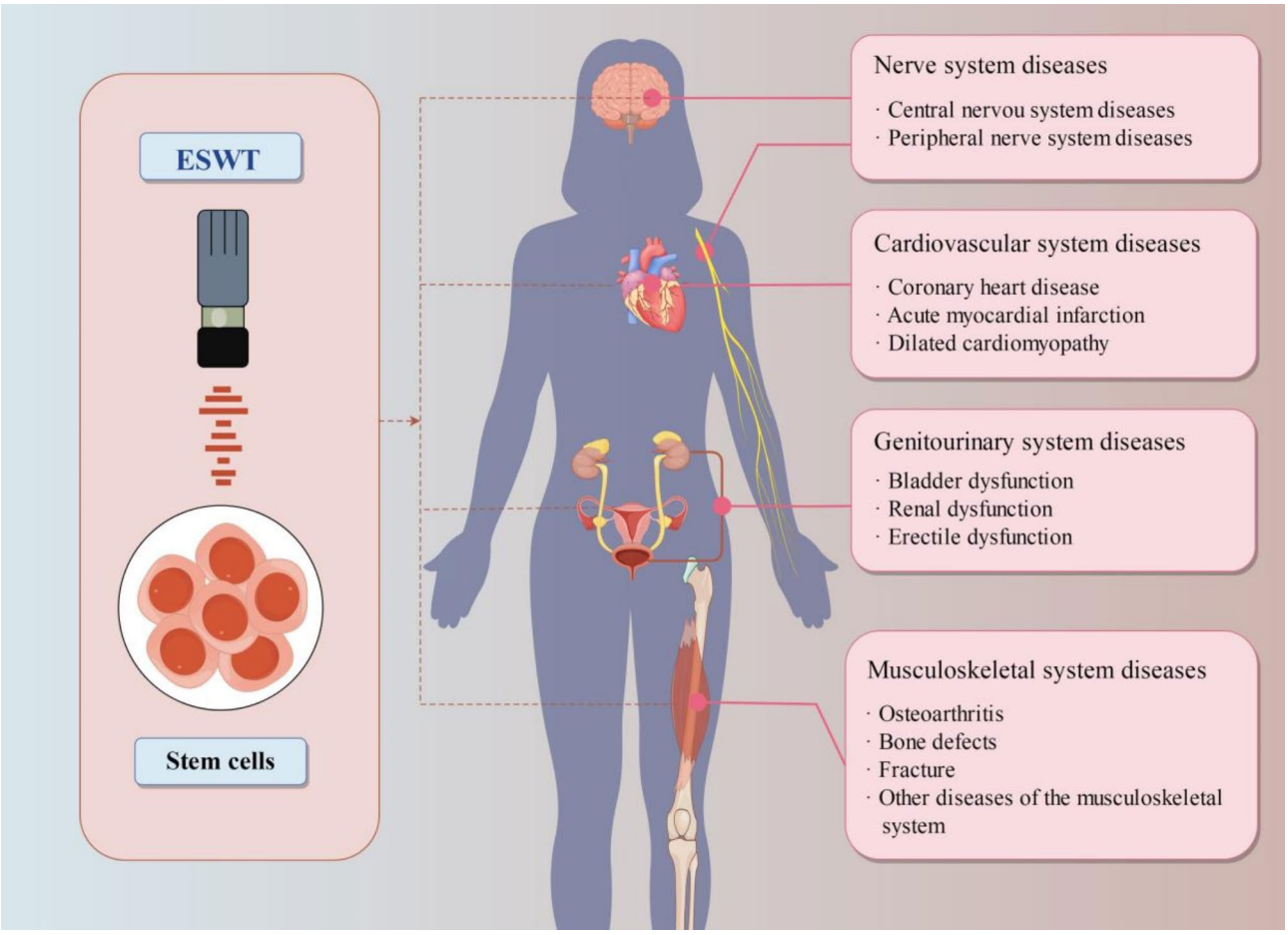

Fig. 2 ESWT is a physical stimulation that applies tensile and compressive stress to tissue cells, converting mechanical signals into biogenic ones. This process triggers healing mechanisms such as anti-inflammation, angiogenesis, and stem cell activation. ESWT can promote the proliferation, differentiation, migration and recruitment of SCs, which can improve the effect of SC therapy for various diseases, including musculoskeletal system diseases, cardiovascular system diseases, genitourinary system diseases and nerve system diseases. (by figure draw)

Application of ESWT on stem cells therapy for musculoskeletal system diseases

Osteoarthritis

Osteoarthritis (OA) is the most common degenerative arthrosis and the leading cause of pain and disorders in the elderly [43]. It is characterized by the destruction of articular cartilage and remodeling of other joint tissues [44]. However, the regenerative ability of articular cartilage is extremely limited due to its non-vascular nature [45, 46]. To address this, a variety of therapies have been used to promote regeneration cartilage tissue regeneration [47, 48]. Due to the limited renewal capacity and matrix generation of chondrocytes after cell expansion, stem cells have emerged as a rational method for promoting cartilage regeneration [49, 50]. Specifically, BMSCs, ADSCs [51], and subchondral bone stem/progenitor cells (SCB-SPCs) [52] are potential options for repairing cartilage tissue. However, they do have several limitations, for instance low proliferative potential, loss of stemness, and the potential for artifactual chromosomal changes [53–55]. Therefore, novel methods to improve the effect of SCs for treating diseases are urgently required.

ESWT has been shown to enhance the therapeutic potential of stem cells [56]. First, ESWT has been shown to enhance cell proliferation and self-renewal in a rabbit study, potentially boosting MSC proliferation by aiding in the transition from the G1 to the S stage of the cell cycle and enhancing the capability of MSCs to repair cartilage impairment [56]. Second, in a rat model of knee osteoarthritis, the combination of ADSCs and ESWT decreases the inflammation-induced levels of TNFα-stimulated gene-6 (TSG-6), proteoglycan-4 (PRG-4), bone morphogenic protein-2 (BMP-2), and bone morphogenetic protein-6 (BMP-6), and enhances the levels of type II collagen and tissue inhibitor of metalloproteinase-1 (TIMP-1), a modulator of matrix metalloproteinase. Thus, the combination of ESWT and ADSCs can inhibit synovitis and improve the damage of Chondral and osteochondral [57]. Additionally, ESWT is able to alleviate the symptoms in OA rats, inhibit cartilage degeneration, and

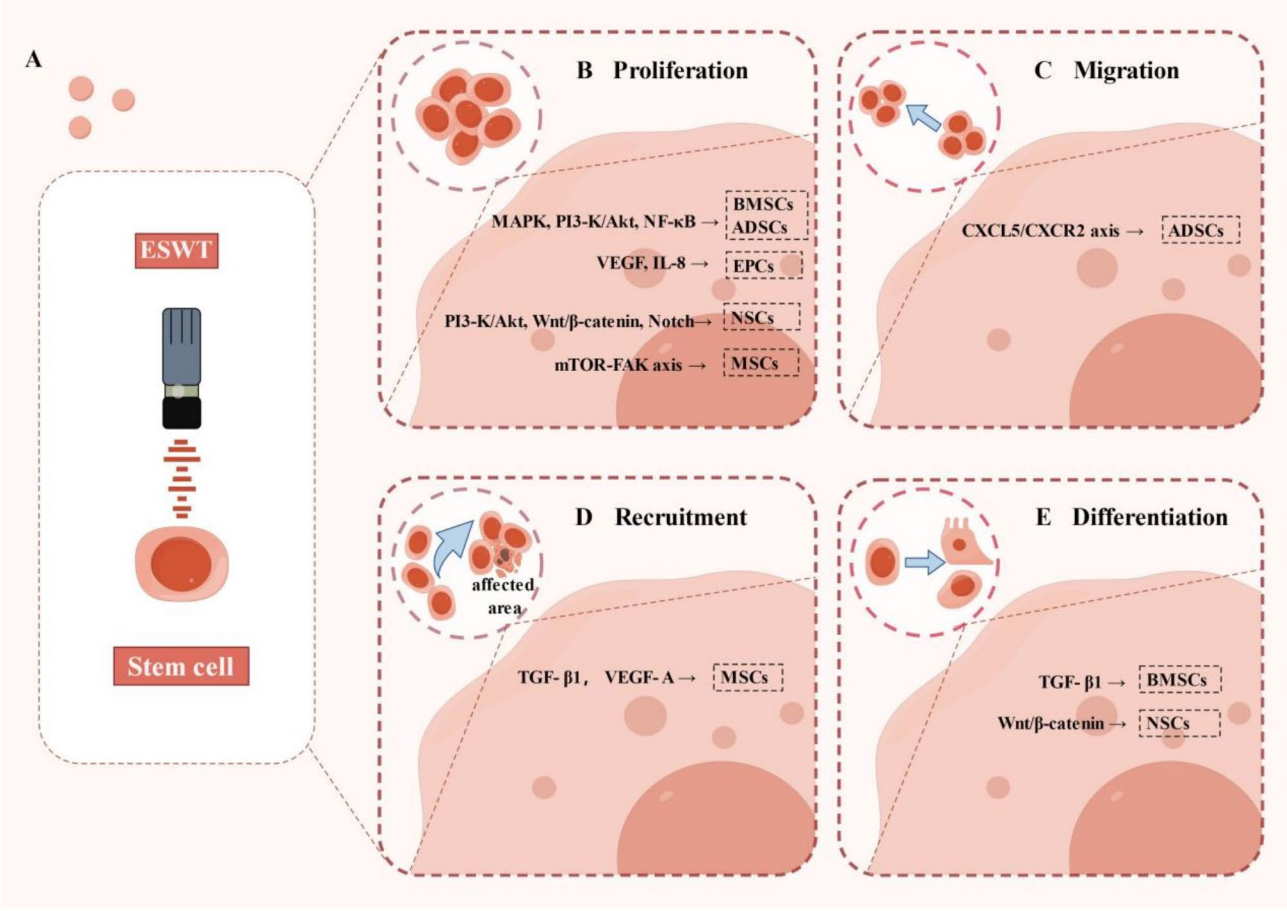

Fig. 3 ESWT can positively influence the biological effects of stem cells, including proliferation, differentiation, migration and recruitment, through various signaling pathways, for instance, MAPK, PI3K/Akt, NF-kB, et al. (by figure draw)

accelerate the repairment of subchondral bone by triggering the Wnt5a/Ca2+signaling pathway in BMSCs [58]. Furthermore, in a model of osteochondral injury, ESWT could potentially enhance the regeneration of SCB-SPCs by activating yes-associated protein (YAP) in vitro and promote the capabilities of SCB-SPCs in vivo [59]. Therefore, utilizing shock waves for modulating stem cell behavior represents a promising approach in facilitating cartilage repair.

Bone defects

Bone defects can result from skeletal diseases, congenital defects, trauma, and tumor excisions which require bone repair [60–63]. The major approaches for repairing bone defects are autografts and allografts. However, the application of autografts is limited due to harvest limitations and donor site injuries [64]. Immunogenic responses from host tissues when using allografts can hinder osteogenesis [65]. To tackle these challenges, advanced tissue engineering techniques have been employed [66]. As one of the tissue engineering methods, stem cell treatment has been used widely in bone tissue engineering. Nevertheless, there are still some unsolved problems. For instance, the apoptosis of transplanted cells limits tissue repair [67]. Consequently, alternative interventions are urgently required to boost the therapeutic effect of stem cells.

Preconditioning with ESWT may be a valuable method to improve the therapeutic potential of MSCs [68]. ESWT enhances the growth of mesenchymal cells and their differentiation into bone-forming cells by upregulating BMP expression in rats with a segmental femoral defect, leading to increased formation of new bone [69]. Moreover, TGF-β1 takes part in the recruitment and differentiation of MSCs, and ESWT can directly or indirectly promote the expression of TGF-β1, thereby promoting the therapeutic effects of MSCs in defect tissue in rats [33]. ESWT can also stimulate the production of certain osteogenic transcription factors in a rat model, for instance, collagen type I, Osterix, Runt-related transcription factor 2, and alkaline phosphatase, leading to the differentiation of BMSCs into osteoblasts [70]. Subsequently, disruption of the membrane due to sound waves and pressure from ESWT induces the generation

of superoxide and TGF-β1, leading to the initiation of a signaling pathway that promotes the differentiation of mesenchymal progenitor cells from human umbilical cord blood into osteogenic cells. This process ultimately improves the healing of femoral segmental bone defects in mice with severe combined immunodeficiency disease [71]. In a rat model, a new method of using ESWT along with injecting teriparatide-loaded hydrogel locally enhances the proliferation, migration, and differentiation of osteoporosis-derived bone marrow mesenchymal stem cells (OP-BMSCs) into osteoblasts in vitro, and significantly enhances the healing of segmental bone defects in vivo [72]. To sum up, ESWT has the potential to improve the proliferation and differentiation of stem cells, which can help in the healing of bone defects.

Fracture

A fracture is defined as a disruption of bone continuity and integrity caused by a specific external force [73]. Although most fractures can heal, nonunion is a common complicating disease of fractures. For example, approximately 10% of tibia fractures fail to heal and require additional interventions [74]. Bone reconstruction surgeries rely on the natural presence of osteoprogenitors and MSCs to provide the necessary osteogenic cells. Nevertheless, in certain situations, these cell populations may be insufficient in number, necessitating the recruitment of stimulatory factors to enhance osteoblast quantity and differentiation capabilities [75]. ESWT, a non-invasive therapy, is a potent stimulator of osteoprogenitor cells, such as BMSCs [34], in vivo, which can enhance the proliferation and osteogenic differentiation potential of MSCs in vitro [41, 76–79]. First of all, ESWT facilitates BMSCs growth and differentiation into osteoprogenitor cells through early O^2-mediated induction of TGF-β1 in an animal model [79]. In addition, ESWT can induce hyperpolarization of human bone marrow stem cells (HBMSCs) membrane and transmit osteogenic differentiation signal via the activation of the Ras pathway, thus promoting osteogenic differentiation of HBMSCs [78]. Besides, ESWT induces the release of adenosine triphosphate (ATP) that activates P38 MAPK signaling through P2×7 receptors in human MSCs, leading to human MSCs osteogenic differentiation [80]. ESWT can enhance the differentiation of MSCs into osteoblastic lineage by activating different signaling pathways like focal adhesion kinase (FAK), extracellular signal-regulated kinases-1/2 (ERK1/2), and Runt-related transcription factor-2 (Runx2) [81]. Overall, ESWT enhances the quantity of osteoprogenitor cells and their ability to differentiate into bone-forming cells, thus providing an alternative therapeutic tool for bone reconstruction.

Other diseases of the musculoskeletal system

In addition to the aforementioned diseases, ESWT has also shown the potential to promote recovery from other diseases by regulating the behavior of stem cells. First, ESWT shows potential as a treatment for avascular necrosis of the femoral head (ANFH) by enhancing the expression of core-binding factor α1 (Cbfα1) through activation of the Ras-regulated MAPK pathway and boosting ALP activity and osteocalcin (OCN) levels, ultimately promoting the proliferation and osteogenic differentiation of MSCs. Moreover, ESWT can also inhibit MSCs adipogenic differentiation by reducing the expression level of peroxisome proliferator-activated receptor gamma (PPARG), which is an effective method for treating ANFH [82]. Second, the use of ESWT or adipose-derived mesenchymal stem cell (ADMSC) therapy resulted in a significant decrease in myoglobin and creatine phosphokinase levels. The combination of extracorporeal cardiac shock waves (ECSWs) and ADMSCs treatment further reduced the expression of these biomarkers in animals with ischemia-reperfusion injury. This indicates that ECSW and ADMSC treatment may be a viable option for acute rhabdomyolysis patients who do not respond to conventional treatment [83]. Third, ESWT can boost the activity, proliferation, migration, and collagen production of remaining cells in the anterior cruciate ligament, as well as the production of collagen, TGF-β, VEGF, and the modulation of BMSCs proliferation, migration, collagen synthesis, and tendon formation, thus improving graft maturation following anterior cruciate ligament reconstruction [84]. Finally, in a rat model of chronic hind limb ischemia, pretreatment with shock waves aids in attracting circulating EPCs by boosting the levels of stromal cell-derived factor-1 (SDF-1) and VEGF, ultimately enhancing the therapeutic efficacy of EPC for patients with chronic ischemia [35]. In summary, ESWT has a wide range of potential applications as a promising method to modulate stem cell behavior, providing new therapeutic avenues for the treatment of a variety of musculoskeletal diseases Table 1.

Application of ESWT on stem cells therapy for cardiovascular system diseases

Coronary heart disease

Coronary heart disease (CHD), as the primary cause of death globally, is characterized by the accumulation of atherosclerotic plaque in the coronary arteries, leading to a narrowing of the artery, thus hindering the normal blood flow to the myocardium [85, 86]. Hypoxia-induced damage to endothelial cells is a key factor in the development of angiocardiopathy, such as CHD [87]. Current treatment options, such as percutaneous coronary intervention and coronary artery bypass grafting, have significantly enhanced symptoms and prognosis for most

Table 1 Application of ESWT on stem cells therapy for musculoskeletal system diseases

Diseases	The type of SCs	Mechanism(molecule or pathway)	Therapeutic effect	Reference number
Osteoarthritis	ADSCs	TSG-6, PRG-4, BMP-2, BMP-6, Type II collagen, Matrix metalloproteinase modulator TIMP-1	Inhibit synovitis and improve the damage of chondral and osteochondral	[57]
	BMSCs	Wnt5a/Ca2 + signaling pathway	Alleviate the symptoms, inhibit cartilage degeneration and accelerate repairment of subchondral bone	[58]
	SCB-SPCs	YAP	Enhance the selfrenewal in vitro and repair efficiency in vivo	[59]
Bone defects	MSCs	BMP	Promotes mesenchymal cell growth and osteogenic differentiation, increasing new bone formation	[69]
	MSCs	TGF-β1	Promote the therapeutic effects of MSCs	[33]
	BMSCs	Collagen type I, Osterix, Runt-related transcription factor 2, Alkaline phosphatase	Induce differentiation of BMSCs into osteoblasts	[70]
	Human umbilical cord blood mesenchymal progenitor cells	Superoxide, TGF-β1	Enhance bone defect healing	[71]
	OP-BMSCs	——	Bone defect healing	[72]
Fracture	BMSCs	TGF-β1	Facilitate the growth of BMSCs and differentiation into osteoprogenitor cells	[79]
	HBMSCs	Ras pathway	Promote osteogenic differentiation of human BMSCs	[78]
	MSCs	ATP, P2×7, P38 MAPK signaling	Human MSCs osteogenic differentiation	[80]
	MSCs	FAK, ERK1/2 and RUNX2.	Promote the process of MSCs differentiating into osteoblastic lineage	[81]
Other diseases of the musculoskeletal system	MSCs	MAPK pathway, Core-binding factor α1 (Cbfα1), ALP, Osteocalcin (OCN), PPARG.	Facilitate the proliferation and osteogenic differentiation of MSCs, inhibiting MSCs adipogenic differentiation. To treat avascular necrosis of the femoral head(ANFH)	[82]
	ADMSCs	Myoglobin(MGB), Creatine phosphokinase(CPK)	Alternative for acute rhabdomyolysis patients who are refractory to traditional therapy	[83]
	BMSCs	TGF-β、 VEGF	Improve graft maturation following anterior cruciate ligament reconstruction	[84]
	EPCs	SDF-1, VEGF	Facilitate the recruitment of circulating EPCs, improving the efficacy of EPC therapy in patients with chronic ischemia	[35]

CHD patients. Nevertheless, it remains important to avoid myocardial ischemia and enhance the well-being of individuals who are ineligible for surgery or still suffer from angina pectoris despite receiving the best possible medical or surgical care [88, 89]. EPCs, originating from bone marrow or peripheral blood, can transport to the ischemic heart muscle and transform into fully developed endothelial cells, contributing to the restoration of the injured vascular endothelium and encouraging the formation of new blood vessels [90–92]. However, CHD can reduce the quantity and hinder the function of EPCs, thus impeding the process of endothelial repair regulated by EPCs [93, 94]. Therefore, other strategies are required to enhance the quantity and function of EPCs.

ESWT, which is a new and noninvasive method, can improve cardiac muscle ischemia and heart function by improving the function of EPCs [95–98]. For instance, ESWT can enhance EPCs function in a rat model by triggering the PI3K/Akt/eNOS signaling pathway and reducing EPCs apoptosis after hypoxic injury [99]. In addition, ESWT elevated the expression of VEGF and IL-8 in the heart muscle deprived of oxygen, leading to the proliferation, differentiation and recruitment of endothelial progenitor cells in a medical study. Besides, after undergoing ESWT, patients with CHD experienced relief in clinical symptoms, as well as improvements in their quality of life and exercise endurance [38]. As a consequence, ESWT enhancement of EPCs function in patients with CHD may be a hopeful strategy for the prevention and treatment of ischaemic heart disease.

Acute myocardial infarction

Acute myocardial infarction (AMI) is the most severe and lethal type of CHD [100], which happens when the main branch of the coronary artery is abruptly obstructed, resulting in ischemia or the death of heart muscle cells [101–103]. Among the various therapies, stem cell therapy plays a positive role in treating heart

ischemia disorder of numerous etiologies, including alleviating ischemic injuries, reducing the severity of angina, and preserving heart function [104–106]. Specifically, utilizing bone marrow stem cell treatment can be advantageous in enhancing heart dysfunction resulting from ischemic events or heart infarction [107–109]. Yet, the extent of cardiac function improvement after different cell therapies remains limited and inadequate in individuals with heart muscle ischemia or acute myocardial infarction [107–112]. Thus, novel and effective therapeutic methods are needed to further promote heart function [113, 114].

During ischemic preconditioning, ESWT enhances the expression of Connexin-43 (Cx43) in cardiomyocyte mitochondria, thereby contributing significantly to the reduction of infarct size [115]. In a rabbit model, the expression of Cx43 and cytochrome C protein in mitochondria can be enhanced by treating bone marrow-derived mononuclear cells (BMDMNCs) with ESWT. Additionally, in a rabbit model, the combination of ESWT with BMDMNCs was found to be more effective than BMDMNC therapy alone in reducing endothelin-1 (ET-1) gene expression and enhancing endothelial nitric oxide synthase (eNOS) gene expression to improve left ventricular (LV) function [116]. The combined application of ESWT and BMDMNCs treatment had a superior effect compared with either ESWT or BMDMNCs treatment in the mini-pig AMI model, including inhibition of heart remodeling, apoptosis and inflammation, decrease in heart infarct size, enhancement of angiogenesis as well as the preservation of heart function [117]. Therefore, ESWT combined with stem cell therapy is a promising therapeutic approach for AMI patients.

Dilated cardiomyopathy

The characteristics of dilated cardiomyopathy (DCM) are LV or biventricular dilation and systolic dysfunction without coronary artery disease, valvular or congenital heart disease [118, 119]. The physiopathological mechanisms of DCM involved aggravative inflammation, oxidative stress, mitochondria (mito) reactive oxygen species production, mito dysfunction [120–126]. Among these mechanisms, mito dysfunction leads to energy exhaustion because of scar generation and the death of myocardial cells [124–128]. The early direct transplantation of mito into LV cardiac muscle of DCM rats not only preserved the function of LV, but also obviously inhibited recipient cells apoptosis, oxidative stress and further mito injury [129]. However, there are some questions regarding mito transplantation, such as the fact that most transplanted mito seem to remain outside of cells. Hence, other strategies are expected to improve the internalization of transplanted mito [130].

ESWT, as an innovative therapy, enhanced the transfer of external mitochondria into the recipient cells both in vitro and in vivo [131, 132]. Moreover, in DCM rats, ESWT-assisted mitochondrial delivery into ADMSCs was more effective than ESWT alone in promoting angiogenesis and reducing heart DCM injury [133]. Overall, combining ESWT with mitochondrial implantation into ADMSCs could provide advantages for DCM patients, especially those with impaired LV function and resistance to conventional treatments Table 2.

Application of ESWT on stem cells therapy for genitourinary system diseases

Bladder dysfunction

Bladder dysfunction can manifest as urinary incontinence, neurogenic bladder or urinary retention [134], including diabetic bladder dysfunction (DBD) and stress urinary incontinence (SUI) et al. Traditional management approaches for DBD focus on relieving symptoms rather than addressing the potential disorders, making it a refractory condition [135]. The therapeutic methods for SUI such as pelvic floor exercises, electrostimulation, sling and artificial urinary sphincter, have demonstrated unsatisfactory effectiveness at present. Therefore, new and effective treatments are urgently needed to restore normal urethral function for the above mentioned disorders [136].

Stem cell treatment holds promise in the treatment of DBD and SUI due to its ability to promote neurovascular muscle regeneration [137, 138]. ADSCs originate from adipose tissue and are a type of mesenchymal stem

Table 2 Application of ESWT on stem cells therapy for cardiovascular system diseases

Diseases	The type of SCs	Mechanism(molecule or pathway)	Therapeutic effect	Reference number
Coronary heart disease	EPCs	PI3K/Akt/eNOS signaling pathway	Promote EPCs function and reduce EPCs apoptosis	[99]
	EPCs	VEGF, IL-8	Promote EPCs proliferation, differentiation and recruitment	[38]
Acute myocardial infarction	BMDMNCs	Cx43, Cytochrome C protein, ET-1, eNOS	Increase eNOS gene level to promote LV function	[116]
	BMDMNCs	——	Inhibition of heart remodeling, apoptosis and inflammation, decrease in heart infarct size, enhancement of angiogenesis as well as the preservation of heart function	[117]
Dilated cardiomyopathy	ADMSCs	——	Promote angiogenesis and alleviate heart DCM injury	[133]

cells. Although bladder function can be partially restored through ADSCs differentiation, promoting cell activity after transplantation remains challenging [139]. Therefore, it is crucial to investigate additional approaches to improve the effectiveness of stem cells in treating DBD and SUI.

As a type of physical therapy of modalities, ESWT has been demonstrated to recruit endogenous stem cells to the site of injury [35, 140, 141] and stimulate local stem cells for the treatment of different urological conditions. ESWT induces the movement of both external ADSCs and internal stem cells toward the bladder by increasing the expression of SDF-1 [135, 137]. Furthermore, ESWT can stimulate ADSCs to secrete more VEGF and nerve growth factor (NGF), promoting revascularization and innervation regenerations, thereby ameliorating urinary function in diabetic rats [137]. Cell experiments show that the protein kinase R-like endoplasmic reticulum kinase/activating transcription factor-4 (PERK/ATF4) pathway plays a role in the therapeutic effects of ESWT, promoting the formation of myotubes by rat urethral muscle-derived stem cells in vitro, demonstrating the potential of ESWT to activate muscle-derived stem cells (MDSCs) in their original location, which can improve stress urinary incontinence [142]. In summary, ESWT could improve the efficacy of stem cells in treating bladder dysfunction through various mechanisms.

Renal dysfunction

Renal dysfunction is characterized by a serum creatinine level that has increased by at least 50% in comparison with the initial creatinine level [143]. Renal ischemia-reperfusion injury (IRI) and atherosclerotic renal artery stenosis (ARAS) are frequent contributors to renal impairment [144, 145]. The main pathological feature of both ARAS and IRI is the damage to vascular endothelial cells. As a result, it has become essential to focus on promoting angiogenesis and restoring capillaries density as key goals for therapy [146, 147]. Because there are currently unmet medical needs for the clinical treatments of IRI and ARAS, finding a new and effective solution is necessary [148, 149].

Stem or progenitor cell therapy has been proven effective in improving renal function after renal ischemia [150]. EPCs aid in the formation of small blood vessels and the growth of new blood vessels by moving, sticking, and substituting impaired endothelial cells, ultimately assisting in the reduction of kidney damage [151–153]. ESWT could strengthen the above mentioned effects of EPCs. ESWT has been shown to increase capillary density in ischemic kidneys by facilitating the mobilization and homing of EPCs from the bone marrow to the narrowed kidney in pigs with ARAS. This effect is achieved through the upregulation of VEGF and Integrin-1β, as well as the stimulation of SDF-1 release [154]. Moreover, the SDF-1/CXCR7 pathway is regulated by ESWT in IRI kidneys, leading to enhanced recruitment of circulating EPCs, as well as improved IRI [155]. In brief, ESWT effectively enhances the mobilization, recruitment, and homing of EPCs, thereby increasing the reparative capacity in kidney tissue.

Erectile dysfunction

Erectile dysfunction (ED) is a persistent or recurrent dysfunction in men to achieve and/or keep penile erection sufficient in sexual intercourse, which is being diagnosed when symptoms persist for at least 3 months [156]. Diabetes mellitus is a frequent contributor to erectile dysfunction, linked to various pathogenic factors like cavernous angiopathy and autonomic neuropathy [157]. At present, phosphodiesterase-5 inhibitors (PDE5i) medications taken by mouth are seen as the primary therapy for individuals with ED [158, 159]. Nevertheless, some individuals with erectile dysfunction caused by diabetes may not have a positive response to this therapy, underscoring the need for exploring other treatment options [160].

Stem cells are a hopeful choice because they can regenerate themselves and transform into different types of cells, including endothelial cells, cavernous smooth muscle cells, and neurons [161]. Stem cell therapy has shown potential as a viable approach for treating ED, either through local engraftment or paracrine signaling [162]. Rats with ED are treated by transplantation of mesenchymal stem cells, such as BMSCs and ADSCs, which are originating from bone marrow and adipose tissue [163, 164]. However, the disadvantage of this treatment approach is the low survival rate of implanted stem cells [165].

ESWT, a new approach in regenerative medicine, aids in the integration of MSCs and enhances their survival rate, ultimately improving the effectiveness of stem cell therapy for ED [166]. First, ESWT has been shown to enhance the survival rate of transplanted BMSCs in the corpus cavernosum, possibly due to increased expression of SDF-1 and stimulation of angiogenesis in diabetic rats with ED [166]. Second, ESWT induces the upregulation of platelet endothelial cell adhesion molecule (PECAM) and SDF-1 in penile tissues of diabetic rats with ED, facilitating the recruitment of MSCs [27]. Additionally, ESWT can increase the expression of VEGF in diabetic rats with ED. VEGF plays a crucial role in improving erectile function by stimulating the PI3K/AKT/mammalian target of rapamycin (mTOR) and nitric oxide/cyclic guanosine monophosphate (NO/cGMP) signaling pathway [10]. In conclusion, the combined treatment of ESWT and MSC therapy exhibits enhanced regenerative and repair properties compared to MSCT alone, offering promising potential as an effective ED treatment Table 3.

Table 3 Application of ESWT on stem cells therapy for genitourinary system diseases

Diseases	The type of SCs	Mechanism(molecule or pathway)	Therapeutic effect	Reference number
Bladder dysfunction	ADSCs	SDF-1	The migration of both exogenous ADSCs and endogenous stem cells toward the bladders is induced	[135, 137]
	ADSCs	VEGF, NGF	Promote revascularization and innervation regenerations, ameliorating urinary function	[137]
	MDSCs	PERK/ATF4 pathway	Promote the formation of myotubes by rat urethral muscle-derived stem cells, improve stress urinary incontinence	[142]
Renal dysfunction (IRI and ARAS)	EPCs	VEGF, Integrin-1β, SDF-1	Promote the mobilization and homing of EPCs, enhance ischemic kidney capillary density	[154]
	EPCs	SDF-1/CXCR7 pathway	Enhanced recruitment of circulating EPCs and improved IRI	[155]
Erectile dysfunction	BMSCs	SDF-1	Promote angiogenesis in diabetic ED rats	[166]
	MSCs	PECAM, SDF-1	Helps in the recruitment of MSCs	[27]
	——	VEGF, PI3K/AKT/mTOR signaling pathway, NO/cGMP signaling pathway	Improvement in erectile function	[10]

Table 4 Application of ESWT on stem cells therapy for nerve system diseases

Diseases	The type of SCs	Mechanism(molecule or pathway)	Therapeutic effect	Reference number
Central nervou system(CNS) and Peripheral nerve system diseases	NSCs	Wnt/β-catenin pathway	Increase in the number of neurons and improve neurological function	[42]
	NSCs	PI3K, AKT, NEAT1-let 7b axis	Promote the proliferation of NSCs	[39, 169]

Application of ESWT on stem cells therapy for nerve system diseases

Neurological disorders, including central nervou system (CNS) and peripheral nerve system (PNS) diseases, are major contributors to global morbidity and mortality. Surgical and pharmaceutical approaches are common treatment modalities for neurological conditions [16, 167, 168]. However, the effectiveness of these interventions is generally unsatisfactory, highlighting the urgent new therapeutic methods.

Recently, stem cell therapy has emerged as a promising treatment for nervous system disorders [169]. The therapeutic mechanism of stem cell therapy involves inhibiting neuroinflammation, promoting neural differentiation and secreting neurotrophic factors [11]. However, a significant drawback in utilizing stem cells (SCs) for nervous system disorders is their restricted abilities in proliferation, differentiation and migration [170]. To address this challenge, ESWT has emerged as a new and promising method to tackle this challenge by stimulating stem cell migration and differentiation with strong regenerative abilities, aiding in tissue regeneration [171]. ESWT has been shown to have a significant impact on the growth and maturation of neural stem cells (NSCs) through the Wnt/β-catenin pathway in a cerebral ischemia rat model [42], resulting in a higher neuron count and ultimately improving neurological function. Furthermore, ESWT can boost the proliferation of NSCs by increasing PI3K and AKT levels and suppressing the nuclear enriched abundant transcript-1 (NEAT1)-let 7b axis in mice [39, 169]. Moreover, the use of ESWT has been shown to promote the growth of new nerve cells, boost the proliferation and differentiation of NSCs, and ultimately enhance the functioning of the nervous system [172]. In summary, the combination of SCs and ESWT is a promising method to treat nerve system diseases Table 4.

Conclusion and perspectives

ESWT is a non-invasive treatment method with significant therapeutic potential and promising clinical applications across various medical fields. In musculoskeletal system diseases, ESWT can enhance cartilage repair, bone defect healing, and fracture reconstruction, thus expediting the recovery process by modulating stem cell behavior. Within cardiovascular system diseases, ESWT effectively alleviates symptoms of coronary heart disease, reduces infarct size post-acute myocardial infarction, and enhances cardiac function in dilated cardiomyopathy through improving the endothelial progenitor cells (EPCs) and other stem cells. Furthermore, ESWT plays a crucial role in urogenital and neurological diseases by recruiting and activating endogenous stem cells to facilitate tissue repair and regeneration, thereby improving patients' symptoms and quality of life. In conclusion, ESWT, as an emerging treatment modality, has demonstrated significant efficacy and

advantages in treating diverse diseases, offering novel therapeutic options and insights to the medical community. With ongoing research and technological advancements, ESWT is poised to be more widely utilized across various fields, delivering improved treatment outcomes and quality of life for patients.

However, two issues need to be noted. First, the research on the impact of ESWT combined with SCs on systemic diseases is still in the early stages and needs more investigation. Second, ESWT can improve the function of stem cells through different mechanisms, such as tissue regeneration, angiogenesis, anti-inflammation, and stem cell activation and recruitment. However, there is no uniform standard for the parameters of ESWT to enhance the effect of SC treatment, including frequency, intensity, timing, duration, and site of stimulation, which should be investigated further in upcoming research. In conclusion, ESWT is a reliable and promising interventional method to promote the effect of SCs on various diseases, which is worthy of further investigation.

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Author contributions
DK, QC, YW, HN, FZ contributed to conception and design of this study; DK, QC, YW, GX, ML, XT, HN, FZ contributed to draft the work or substantively revise it. All authors read and approved the final manuscript.

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References

1. Kolios G, Moodley Y. Introduction to stem cells and regenerative medicine. Respiration. 2013;85(1):3–10.
2. Friedenstein AJ, Gorskaja JF, Kulagina NN. Fibroblast precursors in normal and irradiated mouse hematopoietic organs. Exp Hematol. 1976;4(5):267–74.
3. Friedenstein AJ, et al. Heterotopic of bone marrow. Analysis of precursor cells for osteogenic and hematopoietic tissues. Transplantation. 1968;6(2):230–47.
4. Shimomura T, et al. Hepatic differentiation of human bone marrow-derived UE7T-13 cells: effects of cytokines and CCN family gene expression. Hepatol Res. 2007;37(12):1068–79.
5. Wu GH, et al. Recovery of paralyzed limb motor function in canine with complete spinal cord injury following implantation of MSC-derived neural network tissue. Biomaterials. 2018;181:15–34.
6. Uccelli A, Moretta L, Pistoia V. Mesenchymal stem cells in health and disease. Nat Rev Immunol. 2008;8(9):726–36.
7. Nicodemou A et al. Emerging roles of mesenchymal Stem/Stromal-Cell-derived extracellular vesicles in Cancer Therapy. Pharmaceutics, 2023. 15(5).
8. Zou X, et al. Targeting murine mesenchymal stem cells to kidney Injury Molecule-1 improves their therapeutic efficacy in chronic ischemic kidney Injury. Stem Cells Transl Med. 2018;7(5):394–403.
9. Xue Z, Liao Y, Li Y. Effects of microenvironment and biological behavior on the paracrine function of stem cells. Genes Dis. 2024;11(1):135–47.
10. Zhu GQ, et al. Efficient Promotion of Autophagy and Angiogenesis using mesenchymal stem cell therapy enhanced by the low-energy shock waves in the treatment of Erectile Dysfunction. Stem Cells Int. 2018;2018:p1302672.
11. Wang L, et al. Injectable hyaluronic acid hydrogel loaded with BMSC and NGF for traumatic brain injury treatment. Mater Today Bio. 2022;13:100201.
12. Zhao L, et al. Preconditioning strategies for improving the survival rate and paracrine ability of mesenchymal stem cells in acute kidney injury. J Cell Mol Med. 2019;23(2):720–30.
13. Chen Y, et al. Role and mechanism of micro-energy treatment in regenerative medicine. Transl Androl Urol. 2020;9(2):690–701.
14. Auersperg V, Trieb K. Extracorporeal shock wave therapy: an update. EFORT Open Rev. 2020;5(10):584–92.
15. Surace SJ, et al. Shock wave therapy for rotator cuff disease with or without calcification. Cochrane Database Syst Rev. 2020;3(3):CD008962.
16. Guo J, Hai H, Ma Y. Application of extracorporeal shock wave therapy in nervous system diseases: a review. Front Neurol. 2022;13:963849.
17. van der Worp H, et al. ESWT for tendinopathy: technology and clinical implications. Knee Surg Sports Traumatol Arthrosc. 2013;21(6):1451–8.
18. Chen L, et al. Effect and safety of extracorporeal shockwave therapy for postherpetic neuralgia: a randomized single-blind clinical study. Front Neurol. 2022;13:948024.
19. Moya D, et al. The role of extracorporeal Shockwave Treatment in Musculoskeletal disorders. J Bone Joint Surg Am. 2018;100(3):251–63.
20. Shah N, Morsi Y, Manasseh R. From mechanical stimulation to biological pathways in the regulation of stem cell fate. Cell Biochem Funct. 2014;32(4):309–25.
21. d'Agostino MC, et al. Shock wave as biological therapeutic tool: from mechanical stimulation to recovery and healing, through mechanotransduction. Int J Surg. 2015;24Pt B:p147–53.
22. Simplicio CL, et al. Extracorporeal shock wave therapy mechanisms in musculoskeletal regenerative medicine. J Clin Orthop Trauma. 2020;11(Suppl 3):S309–18.
23. Krol P, et al. Focused and radial shock Wave Therapy in the treatment of tennis elbow: a Pilot Randomised Controlled Study. J Hum Kinet. 2015;47:127–35.
24. Kertzman P, et al. Radial extracorporeal shock wave therapy is efficient and safe in the treatment of fracture nonunions of superficial bones: a retrospective case series. J Orthop Surg Res. 2017;12(1):164.
25. Antebi B, et al. The effect of acute respiratory distress syndrome on bone marrow-derived mesenchymal stem cells. Stem Cell Res Ther. 2018;9(1):251.
26. Tian Y, et al. Mesenchymal stem cells improve mouse non-heart-beating liver graft survival by inhibiting Kupffer cell apoptosis via TLR4-ERK1/2-Fas/FasL-caspase3 pathway regulation. Stem Cell Res Ther. 2016;7(1):157.
27. Qiu X, et al. Effects of low-energy shockwave therapy on the erectile function and tissue of a diabetic rat model. J Sex Med. 2013;10(3):738–46.
28. Kang N, Yu X, Ma Y. Radial extracorporeal shock wave therapy in a patient with decubitus ulcer after spinal cord injury: a case report. Am J Transl Res. 2020;12(5):2093–8.
29. Wang S, et al. Improved Healing of Diabetic Foot Ulcer upon Oxygenation therapeutics through Oxygen-Loading Nanoperfluorocarbon triggered by Radial extracorporeal shock Wave. Oxid Med Cell Longev. 2019;2019:p5738368.
30. Zhang D, et al. Radial extracorporeal shock Wave Therapy as a Novel Agent for Benign Prostatic Hyperplasia Refractory to Current Medical Therapy. Am J Mens Health. 2019;13(1):1557988319831899.
31. Li G, et al. Efficacy of radial extracorporeal shock wave therapy for chronic prostatitis/chronic pelvic pain syndrome: a protocol for systematic review. Med (Baltim). 2020;99(44):e22981.
32. Salcedo-Jimenez R, et al. Extracorporeal shock Wave Therapy enhances the in vitro metabolic activity and differentiation of equine umbilical cord blood mesenchymal stromal cells. Front Vet Sci. 2020;7:554306.
33. Chen YJ, et al. Recruitment of mesenchymal stem cells and expression of TGF-beta 1 and VEGF in the early stage of shock wave-promoted bone regeneration of segmental defect in rats. J Orthop Res. 2004;22(3):526–34.

34. Wang FS, et al. Extracorporeal shock wave promotes growth and differentiation of bone-marrow stromal cells towards osteoprogenitors associated with induction of TGF-beta1. J Bone Joint Surg Br. 2002;84(3):457–61.
35. Aicher A, et al. Low-energy shock wave for enhancing recruitment of endothelial progenitor cells: a new modality to increase efficacy of cell therapy in chronic Hind limb ischemia. Circulation. 2006;114(25):2823–30.
36. Zhao Y, et al. Activation of bone marrow-derived mesenchymal stromal cells-a new mechanism of defocused low-energy shock wave in regenerative medicine. Cytotherapy. 2013;15(12):1449–57.
37. Xu L, et al. Defocused low-energy shock wave activates adipose tissue-derived stem cells in vitro via multiple signaling pathways. Cytotherapy. 2016;18(12):1503–14.
38. Cai HY, et al. Cardiac shockwave therapy improves myocardial function in patients with refractory coronary artery disease by promoting VEGF and IL-8 secretion to mediate the proliferation of endothelial progenitor cells. Exp Ther Med. 2015;10(6):2410–6.
39. Zhang J, et al. Radial extracorporeal shock Wave Therapy enhances the proliferation and differentiation of neural stem cells by Notch, PI3K/AKT, and Wnt/beta-catenin signaling. Sci Rep. 2017;7(1):15321.
40. Lee FY, et al. The mTOR-FAK mechanotransduction signaling axis for focal adhesion maturation and cell proliferation. Am J Transl Res. 2017;9(4):1603–17.
41. Schuh CM, et al. In vitro extracorporeal shock wave treatment enhances stemness and preserves multipotency of rat and human adipose-derived stem cells. Cytotherapy. 2014;16(12):1666–78.
42. Kang N, et al. Radial extracorporeal shock wave therapy improves cerebral blood flow and neurological function in a rat model of cerebral ischemia. Am J Transl Res. 2017;9(4):2000–12.
43. Chen D, et al. Osteoarthritis: toward a comprehensive understanding of pathological mechanism. Bone Res. 2017;5:16044.
44. Loeser RF, et al. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum. 2012;64(6):1697–707.
45. Ito H, et al. Control of articular synovitis for bone and cartilage regeneration in rheumatoid arthritis. Inflamm Regen. 2018;38:7.
46. Qi C, et al. Corrigendum to Photo-crosslinkable, injectable sericin hydrogel as 3D biomimetic extracellular matrix for minimally invasive repairing cartilage [biomaterials 163 (2018) 89–104]. Biomaterials. 2021;278:121134.
47. Anderson JA, et al. Stem cell therapies for knee cartilage repair: the current status of preclinical and clinical studies. Am J Sports Med. 2014;42(9):2253–61.
48. Caldwell KL, Wang J. Cell-based articular cartilage repair: the link between development and regeneration. Osteoarthritis Cartilage. 2015;23(3):351–62.
49. Bhattacharjee M, et al. Tissue engineering strategies to study cartilage development, degeneration and regeneration. Adv Drug Deliv Rev. 2015;84:107–22.
50. Mardones R, Jofre CM, Minguell JJ. Cell therapy and tissue Engineering Approaches for Cartilage Repair and/or regeneration. Int J Stem Cells. 2015;8(1):48–53.
51. Lu L, et al. Treatment of knee osteoarthritis with intra-articular injection of autologous adipose-derived mesenchymal progenitor cells: a prospective, randomized, double-blind, active-controlled, phase IIb clinical trial. Stem Cell Res Ther. 2019;10(1):143.
52. Kruger JP, et al. Proliferation, migration and differentiation potential of human mesenchymal progenitor cells derived from osteoarthritic subchondral cancellous bone. J Stem Cells Regen Med. 2018;14(1):45–52.
53. Bongso A, Fong CY. The therapeutic potential, challenges and future clinical directions of stem cells from the Wharton's jelly of the human umbilical cord. Stem Cell Rev Rep. 2013;9(2):226–40.
54. Pittenger MF, et al. Multilineage potential of adult human mesenchymal stem cells. Science. 1999;284(5411):143–7.
55. Baksh D, Yao R, Tuan RS. Comparison of proliferative and multilineage differentiation potential of human mesenchymal stem cells derived from umbilical cord and bone marrow. Stem Cells. 2007;25(6):1384–92.
56. Zhang H, et al. Radial shockwave treatment promotes human mesenchymal stem cell self-renewal and enhances cartilage healing. Stem Cell Res Ther. 2018;9(1):54.
57. Cheng JH et al. Autologous adipose-derived mesenchymal stem cells combined with Shockwave Therapy synergistically ameliorates the osteoarthritic pathological factors in knee Joint. Pharmaceuticals (Basel), 2021. 14(4).
58. Yu L, et al. Extracorporeal shock Wave rebuilt subchondral bone in vivo and activated Wnt5a/Ca(2+) signaling in Vitro. Biomed Res Int. 2017;2017:p1404650.
59. Zhao Z, et al. Radial extracorporeal shockwave promotes subchondral bone stem/progenitor cell self-renewal by activating YAP/TAZ and facilitates cartilage repair in vivo. Stem Cell Res Ther. 2021;12(1):19.
60. Mikos AG, et al. Engineering complex tissues. Tissue Eng. 2006;12(12):3307–39.
61. Kaigler D, et al. Transplanted endothelial cells enhance orthotopic bone regeneration. J Dent Res. 2006;85(7):633–7.
62. Deville S, et al. Freezing as a path to build complex composites. Science. 2006;311(5760):515–8.
63. Johnson PC, et al. Strategic directions in tissue engineering. Tissue Eng. 2007;13(12):2827–37.
64. Virk MS, et al. Influence of short-term adenoviral vector and prolonged lentiviral vector mediated bone morphogenetic protein-2 expression on the quality of bone repair in a rat femoral defect model. Bone. 2008;42(5):921–31.
65. Gazdag AR, et al. Alternatives to Autogenous Bone Graft: efficacy and indications. J Am Acad Orthop Surg. 1995;3(1):1–8.
66. Vacanti JP, Langer R. Tissue engineering: the design and fabrication of living replacement devices for surgical reconstruction and transplantation. Lancet. 1999;354(Suppl 1):SI32–4.
67. Hwang NS, et al. In vivo commitment and functional tissue regeneration using human embryonic stem cell-derived mesenchymal cells. Proc Natl Acad Sci U S A. 2008;105(52):20641–6.
68. Suhr F, et al. Cell biological effects of mechanical stimulations generated by focused extracorporeal shock wave applications on cultured human bone marrow stromal cells. Stem Cell Res. 2013;11(2):951–64.
69. Wang FS, et al. Temporal and spatial expression of bone morphogenetic proteins in extracorporeal shock wave-promoted healing of segmental defect. Bone. 2003;32(4):387–96.
70. Chen Y, et al. An innovative Approach for enhancing bone defect Healing using PLGA scaffolds seeded with extracorporeal-shock-wave-treated bone marrow mesenchymal stem cells (BMSCs). Sci Rep. 2017;7:44130.
71. Wang FS, et al. Shockwave stimulates oxygen radical-mediated osteogenesis of the mesenchymal cells from human umbilical cord blood. J Bone Min Res. 2004;19(6):973–82.
72. Chen Q, et al. Extracorporeal shock Wave Combined with Teriparatide-Loaded Hydrogel Injection promotes segmental bone defects healing in osteoporosis. Tissue Eng Regen Med. 2021;18(6):1021–33.
73. Zeng C, et al. Stability of internal fixation systems based on different subtypes of Schatzker II fracture of the tibial plateau: a finite element analysis. Front Bioeng Biotechnol. 2022;10:973389.
74. Antonova E, et al. Tibia shaft fractures: costly burden of nonunions. BMC Musculoskelet Disord. 2013;14:42.
75. Alshihri A, et al. The effects of shock wave stimulation of mesenchymal stem cells on proliferation, migration, and differentiation in an injectable gelatin matrix for osteogenic regeneration. J Tissue Eng Regen Med. 2020;14(11):1630–40.
76. Catalano MG, et al. Extracorporeal shockwaves (ESWs) enhance the osteogenic medium-induced differentiation of adipose-derived stem cells into osteoblast-like cells. J Tissue Eng Regen Med. 2017;11(2):390–9.
77. Raabe O, et al. Effect of extracorporeal shock wave on proliferation and differentiation of equine adipose tissue-derived mesenchymal stem cells in vitro. Am J Stem Cells. 2013;2(1):62–73.
78. Wang FS, et al. Physical shock wave mediates membrane hyperpolarization and Ras activation for osteogenesis in human bone marrow stromal cells. Biochem Biophys Res Commun. 2001;287(3):648–55.
79. Wang FS, et al. Superoxide mediates shock wave induction of ERK-dependent osteogenic transcription factor (CBFA1) and mesenchymal cell differentiation toward osteoprogenitors. J Biol Chem. 2002;277(13):10931–7.
80. Sun D, et al. Shockwaves induce osteogenic differentiation of human mesenchymal stem cells through ATP release and activation of P2X7 receptors. Stem Cells. 2013;31(6):1170–80.
81. Hu J, et al. Focal Adhesion Kinase Signaling Mediated the Enhancement of Osteogenesis of Human Mesenchymal Stem cells Induced by extracorporeal shockwave. Sci Rep. 2016;6:20875.
82. Zhai L, et al. Effects of focused extracorporeal shock waves on bone marrow mesenchymal stem cells in patients with avascular necrosis of the femoral head. Ultrasound Med Biol. 2016;42(3):753–62.
83. Yin TC et al. *Combined Therapy with Extracorporeal Shock Wave and Adipose-Derived Mesenchymal Stem Cells Remarkably Improved Acute Ischemia-Reperfusion Injury of Quadriceps Muscle.* Oxid Med Cell Longev, 2018. 2018: p. 6012636.

84. Lu CC, et al. Extracorporeal shock wave promotes activation of anterior cruciate ligament remnant cells and their paracrine regulation of bone marrow stromal cells' proliferation, migration, collagen synthesis, and differentiation. Bone Joint Res. 2020;9(8):458–68.
85. Shahjehan RD, Bhutta BS. *Coronary Artery Disease*, in *StatPearls*. 2024: Treasure Island (FL).
86. Shao C, et al. Coronary artery disease: from mechanism to clinical practice. Adv Exp Med Biol. 2020;1177:1–36.
87. Cheng F, et al. Folic acid attenuates vascular endothelial cell Injury caused by Hypoxia via the inhibition of ERK1/2/NOX4/ROS pathway. Cell Biochem Biophys. 2016;74(2):205–11.
88. Sung PH, et al. The five-Year Clinical and Angiographic Follow-Up outcomes of Intracoronary transfusion of circulation-derived CD34 + cells for patients with end-stage diffuse coronary artery Disease unsuitable for coronary intervention-phase I clinical trial. Crit Care Med. 2018;46(5):e411–8.
89. Kocyigit D, et al. Traditional and alternative therapies for refractory angina. Curr Pharm Des. 2017;23(7):1098–111.
90. Chopra H, et al. Insights into endothelial progenitor cells: origin, classification, potentials, and prospects. Stem Cells Int. 2018;2018:p9847015.
91. Luo S, et al. Endothelial progenitor cells and hypertension: current concepts and future implications. Clin Sci (Lond). 2016;130(22):2029–42.
92. Mehta JL, Szwedo J. Circulating endothelial progenitor cells, microparticles and vascular disease. J Hypertens. 2010;28(8):1611–3.
93. Nollet E, et al. Accelerated cellular senescence as underlying mechanism for functionally impaired bone marrow-derived progenitor cells in ischemic heart disease. Atherosclerosis. 2017;260:138–46.
94. Watt J, et al. The relationship between oxidised LDL, endothelial progenitor cells and coronary endothelial function in patients with CHD. Open Heart. 2016;3(1):e000342.
95. Nishida T, et al. Extracorporeal cardiac shock wave therapy markedly ameliorates ischemia-induced myocardial dysfunction in pigs in vivo. Circulation. 2004;110(19):3055–61.
96. Fukumoto Y, et al. Extracorporeal cardiac shock wave therapy ameliorates myocardial ischemia in patients with severe coronary artery disease. Coron Artery Dis. 2006;17(1):63–70.
97. Uwatoku T, et al. Extracorporeal cardiac shock wave therapy improves left ventricular remodeling after acute myocardial infarction in pigs. Coron Artery Dis. 2007;18(5):397–404.
98. Khattab AA, et al. Extracorporeal cardiac shock wave therapy: first experience in the everyday practice for treatment of chronic refractory angina pectoris. Int J Cardiol. 2007;121(1):84–5.
99. Wang M, et al. Extracorporeal cardiac shock waves Therapy improves the function of endothelial progenitor cells after Hypoxia Injury via activating PI3K/Akt/eNOS Signal Pathway. Front Cardiovasc Med. 2021;8:747497.
100. Ibanez B, et al. Evolving therapies for myocardial ischemia/reperfusion injury. J Am Coll Cardiol. 2015;65(14):1454–71.
101. Stanley W.C. Cardiac energetics during ischaemia and the rationale for metabolic interventions. Coron Artery Dis. 2001;12(Suppl 1):S3–7.
102. Klopsch C, et al. Vimentin-Induced Cardiac mesenchymal stem cells proliferate in the Acute Ischemic Myocardium. Cells Tissues Organs. 2018;206(1–2):35–45.
103. Musher DM, Abers MS, Corrales-Medina VF. Acute infection and myocardial infarction. N Engl J Med. 2019;380(2):171–6.
104. Tendera M, et al. Intracoronary infusion of bone marrow-derived selected CD34 + CXCR4 + cells and non-selected mononuclear cells in patients with acute STEMI and reduced left ventricular ejection fraction: results of randomized, multicentre myocardial regeneration by Intracoronary infusion of selected Population of Stem cells in Acute myocardial infarction (REGENT) trial. Eur Heart J. 2009;30(11):1313–21.
105. Dill T, et al. Intracoronary administration of bone marrow-derived progenitor cells improves left ventricular function in patients at risk for adverse remodeling after acute ST-segment elevation myocardial infarction: results of the reinfusion of enriched progenitor cells and Infarct Remodeling in Acute Myocardial Infarction study (REPAIR-AMI) cardiac magnetic resonance imaging substudy. Am Heart J. 2009;157(3):541–7.
106. Sun CK, et al. Bone marrow-derived mononuclear cell therapy alleviates left ventricular remodeling and improves heart function in rat-dilated cardiomyopathy. Crit Care Med. 2009;37(4):1197–205.
107. Tomita S, et al. Autologous transplantation of bone marrow cells improves damaged heart function. Circulation. 1999;100(19 Suppl):II247–56.
108. Strauer BE, et al. Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans. Circulation. 2002;106(15):1913–8.
109. Yip HK, et al. Autologous bone marrow-derived mononuclear cell therapy prevents the damage of viable myocardium and improves rat heart function following acute anterior myocardial infarction. Circ J. 2008;72(8):1336–45.
110. Tse HF, et al. Angiogenesis in ischaemic myocardium by intramyocardial autologous bone marrow mononuclear cell implantation. Lancet. 2003;361(9351):47–9.
111. Schachinger V, et al. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. N Engl J Med. 2006;355(12):1210–21.
112. Murtuza B, et al. Transplantation of skeletal myoblasts secreting an IL-1 inhibitor modulates adverse remodeling in infarcted murine myocardium. Proc Natl Acad Sci U S A. 2004;101(12):4216–21.
113. Zhang D, et al. Over-expression of CXCR4 on mesenchymal stem cells augments myoangiogenesis in the infarcted myocardium. J Mol Cell Cardiol. 2008;44(2):281–92.
114. Iwakura A, et al. Estradiol enhances recovery after myocardial infarction by augmenting incorporation of bone marrow-derived endothelial progenitor cells into sites of ischemia-induced neovascularization via endothelial nitric oxide synthase-mediated activation of matrix metalloproteinase-9. Circulation. 2006;113(12):1605–14.
115. Boengler K, et al. Connexin 43 in cardiomyocyte mitochondria and its increase by ischemic preconditioning. Cardiovasc Res. 2005;67(2):234–44.
116. Sheu JJ, et al. Shock wave-pretreated bone marrow cells further improve left ventricular function after myocardial infarction in rabbits. Ann Vasc Surg. 2010;24(6):809–21.
117. Sheu JJ, et al. Combined therapy with shock wave and autologous bone marrow-derived mesenchymal stem cells alleviates left ventricular dysfunction and remodeling through inhibiting inflammatory stimuli, oxidative stress & enhancing angiogenesis in a swine myocardial infarction model. Int J Cardiol. 2015;193:69–83.
118. Schultheiss HP, et al. Dilated cardiomyopathy. Nat Rev Dis Primers. 2019;5(1):32.
119. McKenna WJ, Maron BJ, Thiene G. Classification, epidemiology, and Global Burden of Cardiomyopathies. Circ Res. 2017;121(7):722–30.
120. Kotamraju S, et al. Doxorubicin-induced apoptosis in endothelial cells and cardiomyocytes is ameliorated by nitrone spin traps and ebselen. Role of reactive oxygen and nitrogen species. J Biol Chem. 2000;275(43):33585–92.
121. Kurian GA, et al. The role of oxidative stress in Myocardial Ischemia and Reperfusion Injury and Remodeling: Revisited. Oxid Med Cell Longev. 2016;2016:p1656450.
122. Simeunovic D, et al. Evaluation of oxidative stress markers and catecholamine changes in patients with dilated cardiomyopathy before and after cardiopulmonary Exercise Testing. Hellenic J Cardiol. 2015;56(5):394–401.
123. Wang S et al. The role of p38 MAPK in the Development of Diabetic Cardiomyopathy. Int J Mol Sci, 2016. 17(7).
124. Galloway CA, Yoon Y. Mitochondrial dynamics in diabetic cardiomyopathy. Antioxid Redox Signal. 2015;22(17):1545–62.
125. Kubli DA, Gustafsson AB. Unbreak my heart: targeting mitochondrial autophagy in diabetic cardiomyopathy. Antioxid Redox Signal. 2015;22(17):1527–44.
126. Westermeier F, et al. Defective insulin signaling and mitochondrial dynamics in diabetic cardiomyopathy. Biochim Biophys Acta. 2015;1853(5):1113–8.
127. Won S, et al. Noninvasive imaging of myocardial extracellular matrix for assessment of fibrosis. Curr Opin Cardiol. 2013;28(3):282–9.
128. Oh H, Ito H, Sano S. Challenges to success in heart failure: cardiac cell therapies in patients with heart diseases. J Cardiol. 2016;68(5):361–7.
129. Yip HK, et al. Early intramyocardial implantation of exogenous mitochondria effectively preserved left ventricular function in doxorubicin-induced dilated cardiomyopathy rat. Am J Transl Res. 2020;12(8):4612–27.
130. Masuzawa A, et al. Transplantation of autologously derived mitochondria protects the heart from ischemia-reperfusion injury. Am J Physiol Heart Circ Physiol. 2013;304(7):H966–82.
131. Lin KC, et al. Shock Wave Therapy enhances mitochondrial delivery into Target cells and protects against Acute Respiratory Distress Syndrome. Mediators Inflamm. 2018;2018:p5425346.
132. Sun CK, et al. Systemic combined melatonin-mitochondria treatment improves acute respiratory distress syndrome in the rat. J Pineal Res. 2015;58(2):137–50.
133. Sung PH et al. Extracorporeal shock Wave enhanced exogenous mitochondria into adipose-derived mesenchymal stem cells and further preserved heart function in Rat Dilated Cardiomyopathy. Biomedicines, 2021. 9(10).

134. Ritter KE et al. 5-HT3 signaling alters development of sacral neural crest derivatives that innervate the lower urinary tract. Int J Mol Sci, 2021. 22(13).
135. Jin Y, et al. Endogenous stem cells were recruited by Defocused Low-Energy Shock Wave in Treating Diabetic bladder dysfunction. Stem Cell Rev Rep. 2017;13(2):287–98.
136. Lin CS, Lue TF. Stem cell therapy for stress urinary incontinence: a critical review. Stem Cells Dev. 2012;21(6):834–43.
137. Zhang H, et al. A promising therapeutic option for diabetic bladder dysfunction: adipose tissue-derived stem cells pretreated by defocused low-energy shock wave. J Tissue Eng Regen Med. 2019;13(6):986–96.
138. Liu G, et al. A cocktail of growth factors released from a heparin hyaluronic-acid hydrogel promotes the myogenic potential of human urine-derived stem cells in vivo. Acta Biomater. 2020;107:50–64.
139. Zhang H, et al. Adipose tissue-derived stem cells ameliorate diabetic bladder dysfunction in a type II diabetic rat model. Stem Cells Dev. 2012;21(9):1391–400.
140. Tepekoylu C, et al. Shock wave treatment induces angiogenesis and mobilizes endogenous CD31/CD34-positive endothelial cells in a hindlimb ischemia model: implications for angiogenesis and vasculogenesis. J Thorac Cardiovasc Surg. 2013;146(4):971–8.
141. Li Y, et al. Efficacy and safety of Immuno-magnetically sorted smooth muscle progenitor cells derived from Human-Induced pluripotent stem cells for restoring urethral sphincter function. Stem Cells Transl Med. 2017;6(4):1158–67.
142. Wang B, et al. Low-intensity extracorporeal shock wave therapy promotes myogenesis through PERK/ATF4 pathway. Neurourol Urodyn. 2018;37(2):699–707.
143. Becares N, et al. Immune Regulatory mediators in plasma from patients with Acute Decompensation are Associated with 3-Month Mortality. Clin Gastroenterol Hepatol. 2020;18(5):1207–e12156.
144. Jiang Y, Zhang MH. Atherosclerotic renal artery stenosis: how should we do? Chin Med J (Engl). 2021;134(12):1402–4.
145. Levine MH, et al. Class-specific histone/protein deacetylase inhibition protects against renal ischemia reperfusion injury and fibrosis formation. Am J Transpl. 2015;15(4):965–73.
146. Zarbock A, et al. Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: a randomized clinical trial. JAMA. 2015;313(21):2133–41.
147. Puranik AS, et al. Kidney-resident macrophages promote a proangiogenic environment in the normal and chronically ischemic mouse kidney. Sci Rep. 2018;8(1):13948.
148. Zhang Y, et al. Urolithin A alleviates acute kidney injury induced by renal ischemia reperfusion through the p62-Keap1-Nrf2 signaling pathway. Phytother Res. 2022;36(2):984–95.
149. Cooper CJ, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. N Engl J Med. 2014;370(1):13–22.
150. Saad A, Herrmann SM, Textor SC. Chronic renal ischemia in humans: can cell therapy repair the kidney in occlusive renovascular disease? Physiol (Bethesda). 2015;30(3):175–82.
151. Shen WC, et al. Induced pluripotent stem cell-derived endothelial progenitor cells attenuate ischemic acute kidney injury and cardiac dysfunction. Stem Cell Res Ther. 2018;9(1):344.
152. Jabarpour M, et al. Hyperbilirubinemia-induced pro-angiogenic activity of infantile endothelial progenitor cells. Microvasc Res. 2018;118:49–56.
153. Karampinis I, et al. The evaluation of circulating endothelial progenitor cells and related angiogenic markers as prognostic factors in soft-tissue tumors. Eur J Surg Oncol. 2018;44(4):496–501.
154. Zhao Y, et al. Low-energy Shockwave Treatment promotes endothelial progenitor cell homing to the stenotic pig kidney. Cell Transpl. 2020;29:963689720917342.
155. Liu J, et al. Low-energy shock wave pretreatment recruit circulating endothelial progenitor cells to attenuate renal ischaemia reperfusion injury. J Cell Mol Med. 2020;24(18):10589–603.
156. Montorsi F, et al. Summary of the recommendations on sexual dysfunctions in men. J Sex Med. 2010;7(11):3572–88.
157. Yin GN, et al. Establishment of in vitro model of erectile dysfunction for the study of high-glucose-induced angiopathy and neuropathy. Andrology. 2017;5(2):327–35.
158. Phe V, Roupret M. Erectile dysfunction and diabetes: a review of the current evidence-based medicine and a synthesis of the main available therapies. Diabetes Metab. 2012;38(1):1–13.
159. Rendell MS, et al. Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. Sildenafil Diabetes Study Group. JAMA. 1999;281(5):421–6.
160. Jeon SH, et al. Combined treatment with extracorporeal shockwaves therapy and an herbal formulation for activation of penile progenitor cells and antioxidant activity in diabetic erectile dysfunction. Transl Androl Urol. 2020;9(2):416–27.
161. Soebadi MA, et al. Advances in stem cell research for the treatment of male sexual dysfunctions. Curr Opin Urol. 2016;26(2):129–39.
162. Matz EL, et al. Stem cell therapy for Erectile Dysfunction. Sex Med Rev. 2019;7(2):321–8.
163. Ouyang X, et al. MSC-derived exosomes ameliorate erectile dysfunction by alleviation of corpus cavernosum smooth muscle apoptosis in a rat model of cavernous nerve injury. Stem Cell Res Ther. 2018;9(1):246.
164. Nishimatsu H, et al. Adrenomedullin mediates adipose tissue-derived stem cell-induced restoration of erectile function in diabetic rats. J Sex Med. 2012;9(2):482–93.
165. Dong Y, et al. Transplantation of neurotrophin-3-transfected bone marrow mesenchymal stem cells for the repair of spinal cord injury. Neural Regen Res. 2014;9(16):1520–4.
166. Shan HT, et al. Combination of low-energy shock-wave therapy and bone marrow mesenchymal stem cell transplantation to improve the erectile function of diabetic rats. Asian J Androl. 2017;19(1):26–33.
167. Farooqui A, et al. Neurological deterioration and computed tomography perfusion changes with increased time to peak in lacunar stroke. Brain Circ. 2022;8(1):17–23.
168. Li F, et al. Perspectives on benefit of early and prereperfusion hypothermia by pharmacological approach in stroke. Brain Circ. 2022;8(2):69–75.
169. Han K, et al. lncRNA NEAT1-let 7b-P21 axis mediates the proliferation of neural stem cells cultured in vitro promoted by radial extracorporeal shock wave. Regen Ther. 2022;21:139–47.
170. Tan B, et al. Effects of FTY720 (Fingolimod) on proliferation, differentiation, and Migration of Brain-Derived neural stem cells. Stem Cells Int. 2016;2016:p9671732.
171. Mittermayr R, et al. Extracorporeal shock wave therapy (ESWT) for wound healing: technology, mechanisms, and clinical efficacy. Wound Repair Regen. 2012;20(4):456–65.
172. Liu T, et al. Cellular signaling pathways modulated by low-intensity extracorporeal shock wave therapy. Int J Impot Res. 2019;31(3):170–6.

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